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TABLE OF CONTENTS

[Intervention Protocol]

Probiotics for treatment of chronic constipation in children

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ABSTRACT

Objectives

This is a protocol for a Cochrane Review (intervention). The objectives are as follows:

To evaluate the efficacy and safety of probiotics for the management of chronic constipation in children.

BACKGROUND

Description of the condition

Childhood constipation is a very common problem in paediatrics (Van den Berg 2006), with a reported prevalence of 3% in the Western world (Chao 2016). It accounts for 3% of all visits to general paediatric clinics, and up to 25% of visits to paediatric gastroenterologists (Afzal 2011). According to the Rome IV criteria, last updated in 2016, functional constipation is diagnosed when there is no identifiable underlying pathological cause (Hyams 2016). Criteria do vary, but are mostly based on key symptoms, including decreased frequency of defecations, hard or painful bowel movements, faecal incontinence, and large diameter stools (Hyams 2016).

Two decades ago, a team of paediatricians from across the globe met in Rome to standardise the diagnostic criteria for various functional gastroenterological disorders in children. Rome II criteria for children were first published in 1999 (Rasquin-Weber 1999). They were updated as Rome III in 2006, and Rome IV in 2016, with definitions for functional constipation, and other functional disorders (Hyams 2016; Hyman 2006; Rasquin 2006).

To diagnose constipation in children over 4 years old, using the Rome IV criteria, at least two of these symptoms must be present at least once per week for one month, with insufficient criteria for the diagnosis of irritable bowel syndrome (Hyams 2016):

- Two or fewer defecations in the toilet per week;
- History of painful or hard bowel movements;
- History of retentive posturing (standing or sitting with legs straight or stiff), or excessive volitional stool retention (withholding from passing stool);
- History of large diameter stools that can obstruct the toilet;
- Presence of a large faecal mass in the rectum;
- One or more episodes of faecal incontinence per week.

These criteria were amended for infants and toddlers in Rome IV, excluding reference to incontinence or large diameter stools until the child is toilet trained (Zeevenhooven 2017).

Effective management of childhood functional constipation requires a partnership between clinicians and parents, particularly for younger children who cannot accurately report symptoms. Informed by parents' reports and interpretations, since they know their child best, clinicians use their training and experience to differentiate between health and illness (Hyams 2016). To successfully treat functional constipation, clinicians must manage the constipation and its causes, and also the psychological impact that functional childhood constipation can have on children and their families.

Description of the intervention

Probiotics are microorganisms that when ingested, are thought to have beneficial effects on a person's health. Research is ongoing into the use of probiotics in the treatment of various gastrointestinal illnesses, including inflammatory and pathological disorders, functional disorders, and chronic non-pathological disorders. In infants, it has been proposed that supplying probiotic bacteria can redress this balance, and provide a healthier intestinal microbiota landscape, with impact on transit through the gut (Savino 2013). In the context of constipation, it has been proposed that these mechanisms enhance colonic peristalsis, and shorten the transit time through the whole gut (Waller 2011).

How the intervention might work

Experimental studies have shown that constipation is often associated with gut microbiota dysbiosis, which consists of the modified abundance of certain taxa of the colonic microbiome, i.e. the natural balance of gut bacteria has been lost (Attaluri 2010). The use of microorganisms might change the composition of bacterial colonies in the bowel, reduce inflammation, and promote normal gut physiology, thereby, reducing functional symptoms. Some probiotics may influence colonic motility by softening the stool, changing secretion or absorption of water and electrolytes, or both, modifying smooth muscle cell contractions, increasing the production of lactate and short-chain fatty acids, and lowering intraluminal pH (Waller 2011). In addition, since they are essentially a food supplement, probiotics are generally perceived as having a good safety profile, particularly compared with other treatments.

Why it is important to do this review

The management of functional childhood constipation varies internationally, and also between centres within the same region. This reflects the lack of a good evidence base for many current treatment strategies.

Until recently, there had only been minimal research on the use of these agents (Tabbers 2010), with published studies showing conflicting results (Banaszkewicz 2005; Sadeghzadeh 2014).

A number of recent systematic reviews in the wider fields of probiotics and childhood constipation, have demonstrated a rapid rise in published trials in this context (Horvath 2013; Tabbers 2010; Tabbers 2015). To date, there is not a Cochrane Review that examines the role of probiotics for chronic constipation in children. Therefore, it is important to synthesise the evidence, using Cochrane methodology.

International guidelines do not list probiotics as therapy, however, it is clear they are of interest to researchers (Tabbers 2014). In addition, as many probiotics are available without a prescription, clear evidence-based guidelines are key for policymakers and parents, to empower them to make appropriate choices for their children.

OBJECTIVES

To evaluate the efficacy and safety of probiotics for the management of chronic constipation in children.

METHODS

Criteria for considering studies for this review

Types of studies

Randomised controlled trials (RCTs) that compare probiotics to no intervention, placebo, or any other intervention.

If identified, we will include cross-over trials and cluster RCTs.

Types of participants

We will include trials with children and adolescents between the ages of 0 and 18 years, who have been diagnosed with functional constipation, with or without incontinence.

The diagnosis of constipation should be based on consensus criteria (e.g. Rome IV).

We will exclude studies with children suffering from any underlying pathology, such as thyroid abnormalities, Hirschsprung's disease, or those who underwent previous bowel surgery at study entry.

Types of interventions

Probiotics administered in any form (powder, liquid, capsule), through any route (oral or rectal), as a single species or as a cocktail of multiple species (including combination with other agents e.g. synbiotics), compared to no treatment, placebo, or any other intervention. Studies can use probiotics at any dosage, and for any duration deemed appropriate by the primary study. We will consider studies that use probiotics as adjunct therapy and meta-analyse their results where they can be appropriately grouped per main therapy.

Types of outcome measures

The outcomes measures are noted below. We will include the primary outcomes in summary of findings table(s).

Primary outcomes

The primary outcome measures will be:

1. The frequency of defecation (number of stools per week), measured at end of study
2. Global improvement or treatment success, as defined by primary studies, measured at end of study
3. Withdrawal due to adverse events

Secondary outcomes

Secondary outcomes will include:

1. Faecal incontinence, or encopresis, measured at end of study
2. Successful disimpaction, as defined by study, measured at end of study
3. Need for additional therapies during the study period
4. Serious adverse events
5. Adverse events

Search methods for identification of studies

Electronic searches

We will search the following sources from the inception of each database to the date of search, by combining terms related to probiotics and constipation, with no restrictions on the language of publication:

- Cochrane Central Register of Controlled Trials (CENTRAL via Ovid Evidence-Based Medicine Reviews Database (EBMR); Appendix 1);
- MEDLINE Ovid (from 1946; Appendix 2);
- Embase Ovid (from 1974; Appendix 3);
- PsycINFO Ovid (from 1806; Appendix 4);
- CINAHL (Cumulative Index to Nursing and Allied Health Literature EBSCO (from 1937; Appendix 5);
- AMED (Allied and Complementary Medicine database Ovid (from 1985; Appendix 6);
- ClinicalTrials.gov (www.clinicaltrials.gov);
- World Health Organization International Clinical Trials Registry Platform (ICTRP; www.who.int/trialsearch/).

We will not impose any date or language restrictions on the searches. Studies published in a non-English language will be professionally translated in full. We will collate references and remove any duplicates.

Searching other resources

Reference Searching

We will inspect the references of all identified studies for more trials.

Personal contacts

We will contact leaders in the field to try and identify other studies. We will identify at least three from presentations and keynote addresses at major international meetings.

Manufacturers

We will contact manufacturers of probiotic agents to try and identify other studies.

Grey Literature

We will search Google, Google Scholar, and OpenGrey, using the main search terms. We will handsearch conference proceedings from the Digestive Disease Week (DDW), United European Gastroenterology Week (UEGW), and European Society for Paediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN) annual scientific meetings from the past two years to identify other potentially relevant studies that may not be published in full. We will only include studies from the grey literature if sufficient data are presented to enable an inclusion decision.

Concerns have previously been raised regarding the accuracy of data presented in abstract publications (Pitkin 1999). Therefore, when we identify references for relevant unpublished or ongoing studies, we will attempt to collect sufficient information to incorporate them in this review. If data are incomplete, we will contact the authors to verify the eligibility of the study, and only include it if they provide suitable data to enable us to assess quality and outcomes. We will conduct sensitivity analysis to determine if this impacts results.

Data collection and analysis

We will carry out data collection and analysis according to the methods recommended in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2020).

Selection of studies

Two review authors (CW and MG) will independently screen titles, abstracts, and full reports for eligibility against the inclusion criteria. The authors will discuss and resolve disagreement by consensus.

Screening abstracts and titles, the two review authors will identify reports that appear to be potentially relevant. We will obtain the full-text reports of those that appear to be potentially relevant. After reading the full texts, the two review authors will independently assess the eligibility of trials, based on the inclusion criteria above and develop a PRISMA flowchart (Page 2021).

Data extraction and management

We will develop data extraction forms a priori as per the recommendations in the *Cochrane Handbook for Systematic Reviews* to extract information on relevant features and results of included studies (Higgins 2020). Two review authors will extract and record data on the data extraction form. We will extract the following data:

- characteristics of children: age, sex, duration of symptoms;
- inclusion and exclusion criteria
- study methods, total number of children originally assigned to each treatment group;
- intervention: preparations, dose, administration regimen;
- control: placebo, other drugs;
- concurrent medications;
- outcomes (time of assessment, length of follow-up, frequency of defecation, pain or straining on defecation, faecal incontinence, stool consistency, need for additional therapies, number and type of adverse events associated with treatment, adverse events); and
- withdrawals and reasons for withdrawals.

Assessment of risk of bias in included studies

Two review authors will independently assess all studies meeting the inclusion criteria for their risk of bias, using criteria outlined in the *Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0* (Higgins 2011). The domains will be:

- sequence generation (selection bias);
- allocation concealment (selection bias);
- blinding of participants and personnel (performance bias);
- blinding of outcome assessment (detection bias);
- incomplete outcome data (attrition bias);
- selective reporting (reporting bias);
- other bias, such as imbalance in participants' baseline characteristics.

We will judge the studies to be at low, high, or unclear risk of bias for each domain assessed, based on the guidance in the *Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0* (Higgins 2011).

After data extraction, the two review authors will compare the extracted data and discuss and resolve discrepancies before the data are transferred into the 'Characteristics of included studies' table.

For cluster-RCTs, we intend to judge risk of bias as prescribed in Section 16.3.2 of the *Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0* (Higgins 2011)

Measures of treatment effect

Dichotomous outcomes

We will assess all dichotomous outcomes by calculating the risk ratio (RR) and 95% CI, using a random-effects model.

Continuous outcomes

We will assess all secondary outcomes calculating the mean difference (MD) and 95% confidence interval (CI), when using the same units. When different scales are used to evaluate the same outcome, we will calculate the standardised mean difference (SMD) and 95% CI. We will pool studies using a random-effects model.

Unit of analysis issues

The participant will be the unit of analysis. For studies comparing more than two intervention groups, we will make multiple pair-wise comparisons between all possible pairs of intervention groups. To avoid double-counting, we will divide shared intervention groups evenly among the comparisons. For dichotomous outcomes, we will divide both the number of events and the total number of participants. For continuous outcomes, we will only divide the total number of participants and leave the means and standard deviations unchanged.

We will include cross-over studies, but only pool data if they are separately reported before and after the cross over; we will only use data from the pre-cross-over phase.

We do not anticipate finding any cluster-RCTs; however, if we do, we will only use study data if the trial authors have used appropriate statistical methods that take the clustering effect into account. We will conduct a sensitivity analysis by excluding cluster-RCTs, to assess the impact on the results.

Dealing with missing data

We will contact authors, when there are missing data, or studies have not reported data in sufficient detail. We will attempt to estimate missing standard deviations using relevant statistical tools and calculators available in Review Manager 5 if studies report standard errors (Review Manager 2020). Studies that fail to report measures of variance will be judged at high risk of selective reporting bias.

Assessment of heterogeneity

We will scrutinise studies to ensure that they are clinically homogeneous in terms of participants, intervention, comparator, and outcome. To test for statistical heterogeneity, we will use a Chi^2 test using a P value of less than 0.1 to give an indication of the presence of heterogeneity. We will quantify consistency as represented by the I^2 statistic. We will interpret the thresholds as follows (Higgins 2020):

- 0% to 40%: might not be important;
- 30% to 60%: may represent moderate heterogeneity;
- 50% to 90%; may represent substantial heterogeneity;
- 75% to 100%: considerable heterogeneity.

We will examine possible explanations for heterogeneity when sufficient data are available, exploring factors such as participant characteristics (e.g. age, sex), condition severity, healthcare system, and country.

We will not pool data in a meta-analysis if we detect a considerable degree of statistical heterogeneity (I^2 > 75%). In cases of considerable statistical heterogeneity, we will investigate whether this can be explained by clinical, methodological, or risk of bias grounds, in which case, we will perform sensitivity analyses excluding identified studies, with reasons. If we cannot find any such reasons for the considerable statistical heterogeneity, we will present the results narratively, in detail.

Assessment of reporting biases

An inclusive search strategy will minimise most reporting biases. We will investigate publication bias using a funnel plot if there are 10 or more studies. We will determine the magnitude of publication bias by visual inspection of the asymmetry of the funnel plot. In addition, we will test funnel plot asymmetry by conducting a linear regression of intervention effect estimate against its standard error, weighted by the inverse of the variance of the intervention effect estimate (Egger 1997).

Data synthesis

We will combine data from individual trials into a meta-analysis if the interventions, participant groups, and outcomes are sufficiently similar (determined by consensus). We will calculate the pooled RR and corresponding 95% CI for dichotomous outcomes, and MD or SMD and corresponding 95% CI for continuous outcomes. We will use a random-effects model for meta-analysis. We will not pool data in meta-analysis if we detect considerable heterogeneity is detected (i.e. I^2 > 75%).

We will use Review Manager 5 software for data analysis (Review Manager 2020). We will analyse data according to the intention-to-treat principle. We will assume that participants with missing final outcomes are treatment failures. We will group analyses by length of follow-up.

Subgroup analysis and investigation of heterogeneity

We will conduct subgroup analyses to study the effects of a number of variables on the outcomes, including:

a. specific probiotic preparation;
b. the effect of length of therapy and follow-up;
c. what, if anything, was initially allowed in the protocol to clear any impaction (such as enemas);
d. age of participants (Infants, non-toilet trained toddlers, older children and adolescents, as per Rome IV criteria (Hyams 2016)).

Sensitivity analysis

Where possible, we will undertake a sensitivity analysis on the primary outcomes to assess whether the findings of the review are robust, based on the decisions made during the review process. In particular, we will exclude studies at high or unclear risk of selection bias due to allocation bias and performance bias, from analyses that include studies with different risk of bias judgments.

Where data analyses include studies with reported and estimated standard deviations, we will exclude those with estimated standard deviations, to assess whether this affects the findings of the review. We will investigate whether the choice of model (fixed-effect versus random-effects) may affect results, as well as studies published in full versus abstract format.

Summary of findings and assessment of the certainty of the evidence

We will present the main results in a summary of findings table. We will export data for each comparison and primary outcome from RevMan 5 to GRADEpro GDT software to assess the certainty of the evidence (GRADEpro GDT).

Data permitting, we will present two summary of findings tables in the following hierarchy:

1. Probiotics versus placebo,
2. Probiotics and osmotic laxative versus osmotic laxative.

If the data reveals more comparison interventions versus probiotics we will add summary of findings tables accordingly.

We will include all three primary outcomes and the secondary outcome 'serious adverse events' .

Based on risk of bias, inconsistency, imprecision, indirectness, and publication bias, we will grade the certainty of the evidence for each outcome as high, moderate, low, or very low. We will justify all decisions to downgrade the certainty of studies using footnotes, and we will make comments to aid the reader's understanding of the review where necessary.

GRADE Working Group grades of evidence

High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: we are moderately confident in the effect estimate; the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: our confidence in the effect estimate is limited; the true effect may be substantially different from the estimate of the effect.
Very low certainty: we have very little confidence in the effect estimate; the true effect is likely to be substantially different from the estimate of effect.

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Low certainty: our confidence in the effect estimate is limited; the true effect may be substantially different from the estimate of the effect.
Very low certainty: we have very little confidence in the effect estimate; the true effect is likely to be substantially different from the estimate of effect.

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APPENDICES

Appendix 1. CENTRAL search strategy

1. exp Probiotics/
2. (probiotic or probiotics).tw,kw.
3. exp Saccharomyces/
4. (Saccaromyce* or boulardii).tw,kw.
5. exp Lactobacillus/
6. (lactobacil* or Betabacterium or Lactobacteria or lactic acid bacteria or casei or paracasei or rhamnosus or helveticus or acidophilus).tw,kw.
7. exp Bifidobacterium/
8. Bifidobacter*.tw,kw.
9. exp Escherichia coli/
10. (Escherichia coli or "E.Coli" or "E. Coli" or Mutaflor or Colinfant).tw,kw.
11. exp Streptococcus/
12. (Streptococcus or Streptococceae or "VSL#3" or "VSL #3").tw,kw.
13. exp Bacillus/
14. Bacillus.tw,kw.
15. exp Clostridium butyricum/
16. clostridium butyricum.tw,kw.
17. exp Enterococcus/
18. (enterococcus or faecalis).tw,kw.
19. ("Biok+" or Lacidofil or Lactogermine or Pb Probinul or BIfido Triple).tw,kw.
20. (Commensal* or yeast or Fung*).tw,kw.
21. or/1-20
22. exp Constipation/
23. constipation.tw,kw.
24. ((fecal or faecal) adj3 (impaction or retention or evacuation)).tw,kw.
25. ((bowel or intestinal) adj3 (delayed or retention or evacuation or function* or habit* or movement* or symptom* or motility)).tw,kw.
26. (obstipation or colon transit or defecation or defaecation).tw,kw.
27. or/22-26
28. 21 and 27
29. exp Adolescent/
30. exp Child/
31. exp Infant/
32. exp Minors/
33. exp Pediatrics/
34. exp Puberty/
35. exp Schools/
36. (baby or babies or child or children or pediatric* or paediatric* or peadiatric* or infan* or neonat* or newborn* or new born* or kid or kids or adolescen* or preschool or pre-school or toddler*).tw,kw.
37. (postmatur* or prematur* or preterm* or preemie or perinat* or boy* or girl* or teen* or minors or prepubescen* or postpubescen* or prepuberty* or pubescen* or puber*).tw,kw.

38. (elementary school* or high school* or highschool* or kinder* or Jugend* or nursery school* or primary school* or secondary school*).tw,kw.
39. (youth* or young or student* or juvenil* or school age* or underage* or schoolchild* or (under* adj age*) or under 16 or under 18).tw,kw.
40. or/29-39
41. 28 and 40

Appendix 2. MEDLINE search strategy

1. exp Probiotics/
2. (probiotic or probiotics).tw,kw.
3. exp Saccharomyces/
4. (Saccaromyce* or boulardii).tw,kw.
5. exp Lactobacillus/
6. (lactobacil* or Betabacterium or Lactobacteria or lactic acid bacteria or casei or paracasei or rhamnosus or helveticus or acidophilus).tw,kw.
7. exp Bifidobacterium/
8. Bifidobacter*.tw,kw.
9. exp Escherichia coli/
10. (Escherichia coli or "E.Coli" or "E. Coli" or Mutaflor or Colinfant).tw,kw.
11. exp Streptococcus/
12. (Streptococcus or Streptococceae or "VSL#3" or "VSL #3").tw,kw.
13. exp Bacillus/
14. Bacillus.tw,kw.
15. exp Clostridium butyricum/
16. clostridium butyricum.tw,kw.
17. exp Enterococcus/
18. (enterococcus or faecalis).tw,kw.
19. ("Biok+" or Lacidofil or Lactogermine or Pb Probinul or BIfido Triple).tw,kw.
20. (Commensal* or yeast or Fung*).tw,kw.
21. or/1-20
22. exp Constipation/
23. constipation.tw,kw.
24. ((fecal or faecal) adj3 (impaction or retention or evacuation)).tw,kw.
25. ((bowel or intestinal) adj3 (delayed or retention or evacuation or function* or habit* or movement* or symptom* or motility)).tw,kw.
26. (obstipation or colon transit or defecation or defaecation).tw,kw.
27. or/22-26
28. 21 and 27
29. exp Adolescent/
30. exp Child/
31. exp Infant/
32. exp Minors/
33. exp Pediatrics/
34. exp Puberty/
35. exp Schools/
36. (baby or babies or child or children or pediatric* or paediatric* or peadiatric* or infan* or neonat* or newborn* or new born* or kid or kids or adolescen* or preschool or pre-school or toddler*).tw,kw.
37. (postmatur* or prematur* or preterm* or preemie or perinat* or boy* or girl* or teen* or minors or prepubescen* or postpubescen* or prepuberty* or pubescen* or puber*).tw,kw.
38. (elementary school* or high school* or highschool* or kinder* or Jugend* or nursery school* or primary school* or secondary school*).tw,kw.
39. (youth* or young or student* or juvenil* or school age* or underage* or schoolchild* or (under* adj age*) or under 16 or under 18).tw,kw.
40. or/29-39
41. 28 and 40
42. randomized controlled trial.pt.

43.controlled clinical trial.pt.
44.randomized.ab.
45.placebo.ab.
46.drug therapy.fs.
47.randomly.ab.
48.trial.ab.
49.groups.ab.
50.or/42-49
51.exp animals/ not humans.sh.
52.50 not 51
53.41 and 52

Note: lines 42 to 52. RCT filter. Cochrane Highly Sensitive Search Strategy for identifying randomized trials in MEDLINE: sensitivity-maximizing version (2008 revision); Ovid format

Appendix 3. Embase search strategy

1. exp probiotic agent/
2. (probiotic or probiotics).tw,kf.
3. exp Saccharomyces/
4. (Saccaromyce* or boulardii).tw,kf.
5. exp Lactobacillus/
6. (lactobacil* or Betabacterium or Lactobacteria or lactic acid bacteria or casei or paracasei or rhamnosus or helveticus or acidophilus).tw,kf.
7. exp Bifidobacterium/
8. Bifidobacter*.tw,kf.
9. exp Escherichia coli/
10. (Escherichia coli or "E.Coli" or "E. Coli" or Mutaflor or Colinfant).tw,kf.
11. exp Streptococcus/
12. (Streptococcus or Streptococceae or "VSL#3" or "VSL #3").tw,kf.
13. exp Bacillus/
14. Bacillus.tw,kf.
15. exp Clostridium butyricum/
16. clostridium butyricum.tw,kf.
17. exp enterococcus/
18. (enterococcus or faecalis).tw,kf.
19. ("Biok+" or Lacidofil or Lactogermine or Pb Probinul or BIfido Triple).tw,kf.
20. (Commensal* or yeast or Fung*).tw,kf.
21. or/1-20
22. exp constipation/
23. constipation.tw,kf.
24. ((fecal or faecal) adj3 (impaction or retention or evacuation)).tw,kf.
25. ((bowel or intestinal) adj3 (delayed or retention or evacuation or function* or habit* or movement* or symptom* or motility)).tw,kf.
26. (obstipation or colon transit or defecation or defaecation).tw,kf.
27. or/22-26
28. 21 and 27
29. exp adolescence/ or exp adolescent/
30. exp child/
31. exp newborn/
32. exp kindergarten/
33. exp pediatrics/
34. exp puberty/
35. exp nursery school/ or exp primary school/ or exp middle school/ or exp high school/ or exp school/

36. (baby or babies or child or children or pediatric* or paediatric* or peadiatric* or infan* or neonat* or newborn* or new born* or kid or kids or adolescen* or preschool or pre-school or toddler*).kw,kf.
37. (postmatur* or prematur* or preterm* or preemie or perinat* or boy* or girl* or teen* or minors or prepubescen* or postpubescen* or prepuberty* or pubescen* or puber*).kw,kf.
38. (elementary school* or high school* or highschool* or kinder* or Jugend* or nursery school* or primary school* or secondary school*).kw,kf.
39. (youth* or young or student* or juvenil* or school age* or underage* or schoolchild* or (under* adj age*) or under 16 or under 18).kw,kf.
40. or/29-39
41. 28 and 40
42. random:.tw.
43. placebo:.mp.
44. double-blind:.tw.
45. or/42-44
46. exp animal/ not human.sh.
47. 45 not 46
48. 41 and 47

Note: lines 42 to 45. Hedge Best balance of sensitivity and specificity filter for identifying randomized trials in Embase. https://hiru.mcmaster.ca/hiru/HIRU_Hedges_EMBASE_Strategies.aspx

Appendix 4. PsycINFO search strategy

1. (probiotic or probiotics).tw.
2. (Saccaromyce* or boulardii).tw.
3. (lactobacil* or Betabacterium or Lactobacteria or lactic acid bacteria or casei or paracasei or rhamnosus or helveticus or acidophilus).tw.
4. Bifidobacter*.tw.
5. (Escherichia coli or "E.Coli" or "E. Coli" or Mutaflor or Colinfant).tw.
6. (Streptococcus or Streptococceae or "VSL#3" or "VSL #3").tw.
7. Bacillus.tw.
8. clostridium butyricum.tw.
9. (enterococcus or faecalis).tw.
10. ("Biok+" or Lacidofil or Lactogermine or Pb Probinul or BIfido Triple).tw.
11. (Commensal* or yeast or Fung*).tw.
12. or/1-11
13. exp Constipation/
14. constipation.tw.
15. ((fecal or faecal) adj3 (impaction or retention or evacuation)).tw.
16. ((bowel or intestinal) adj3 (delayed or retention or evacuation or function* or habit* or movement* or symptom* or motility)).tw.
17. (obstipation or colon transit or defecation or defaecation).tw.
18. or/13-17
19. 12 and 18
20. exp Pediatrics/
21. exp Puberty/
22. exp Schools/
23. (baby or babies or child or children or pediatric* or paediatric* or peadiatric* or infan* or neonat* or newborn* or new born* or kid or kids or adolescen* or preschool or pre-school or toddler*).tw.
24. (postmatur* or prematur* or preterm* or preemie or perinat* or boy* or girl* or teen* or minors or prepubescen* or postpubescen* or prepuberty* or pubescen* or puber*).tw.
25. (elementary school* or high school* or highschool* or kinder* or Jugend* or nursery school* or primary school* or secondary school*).tw.
26. (youth* or young or student* or juvenil* or school age* or underage* or schoolchild* or (under* adj age*) or under 16 or under 18).tw.
27. or/20-26
28. 19 and 27

Appendix 5. CINAHL search strategy

1. S8 S4 AND S6 Limiters - Exclude MEDLINE records; Age Groups: Adolescent: 13-18 years, All Infant, All Child
2. S7 S4 AND S6
3. S6 S4 OR S5
4. S5 (MM "Constipation")
5. S4 TX (constipation or ((fecal or faecal) and (impaction or retention or evacuation))) OR TX (((bowel or intestinal) and (delayed or retention or evacuation or function* or habit* or movement* or symptom* or motility))) AND TX (obstipation or colon transit or defecation or defaecation)
6. S3 S1 OR S2
7. S2 (MM "Probiotics")
8. S1 TX (probiotic or probiotics or Saccaromyce* or boulardii or lactobacil* or Betabacterium or Lactobacteria or lactic acid bacteria or casei or paracasei or rhamnosus or helveticus or acidophilus or Bifidobacter* or Escherichia coli or "E.Coli" or "E. Coli" or Mutaflor or Colinfant or Streptococcus or Streptococceae or "VSL#3" or "VSL #3" or Bacillus or clostridium butyricum) OR TX (enterococcus or faecalis or "Biok+" or Lacidofil or Lactogermine or Pb Probinul or BIfido Triple or Commensal* or yeast or Fung*)

Appendix 6. AMED search strategy

1. (probiotic or probiotics).tw.
2. (Saccaromyce* or boulardii).tw.
3. (lactobacil* or Betabacterium or Lactobacteria or lactic acid bacteria or casei or paracasei or rhamnosus or helveticus or acidophilus).tw.
4. Bifidobacter*.tw.
5. (Escherichia coli or "E.Coli" or "E. Coli" or Mutaflor or Colinfant).tw.
6. (Streptococcus or Streptococceae or "VSL#3" or "VSL #3").tw.
7. Bacillus.tw.
8. clostridium butyricum.tw.
9. (enterococcus or faecalis).tw.
10. ("Biok+" or Lacidofil or Lactogermine or Pb Probinul or BIfido Triple).tw.
11. (Commensal* or yeast or Fung*).tw.
12. or/1-11
13. exp Constipation/
14. constipation.tw.
15. ((fecal or faecal) adj3 (impaction or retention or evacuation)).tw.
16. ((bowel or intestinal) adj3 (delayed or retention or evacuation or function* or habit* or movement* or symptom* or motility)).tw.
17. (obstipation or colon transit or defecation or defaecation).tw.
18. or/13-17
19. 12 and 18
20. exp Pediatrics/
21. exp Puberty/
22. exp Schools/
23. (baby or babies or child or children or pediatric* or paediatric* or peadiatric* or infan* or neonat* or newborn* or new born* or kid or kids or adolescen* or preschool or pre-school or toddler*).tw.
24. (postmatur* or prematur* or preterm* or preemie or perinat* or boy* or girl* or teen* or minors or prepubescen* or postpubescen* or prepuberty* or pubescen* or puber*).tw.
25. (elementary school* or high school* or highschool* or kinder* or Jugend* or nursery school* or primary school* or secondary school*).tw.
26. (youth* or young or student* or juvenil* or school age* or underage* or schoolchild* or (under* adj age*) or under 16 or under 18).tw.
27. or/20-26
28. 19 and 27

HISTORY

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CONTRIBUTIONS OF AUTHORS

MG conceived the review, and MG and CW led the writing. All authors contributed substantially to the planning, writing, and completion of this work.

DECLARATIONS OF INTEREST

CW has none to declare.

MG - Since August 2016, I received travel fees to attend international scientific and training meetings from Pharma companies. These grants included no honoraria, inducement, advisory role, or any other relationship, and were restricted to the travel and meeting-related costs of attending such meetings. The companies include: Biogaia (2017 to 2019), Ferring (2018), Allergan (2017), Synergy (bankrupt in 2018), and Tillots (2017 to 2019). None of these companies had any involvement in any works completed by me, and I have never had any payment for any other activities for them, as confirmed below. From these date onwards, I have made a personal undertaking to take no further funds from any pharmaceutical or formula company in any form, for travel or other related activities. This is to lift the limitations such funding has on my ability to act as a first and corresponding author on reviews, in line with the Cochrane policies on such matters, and is reported in line with these policies.

AA has none to declare.

MS - He acted as a consultant for various pharmaceutical companies in the past, including Forest, Quintiles, Ardelyx, QOL, Sucampo, Allakos, and Allergan.

ALC has none to declare.

LFR has none to declare.

AF acted as a consultant for QOL Medical 2018 to 2019.

LFV has none to declare.

CA has none to declare.

GH has none to declare.

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VS has none to declare.

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